Annual Reporting Form for SCEDDBO Projects and Cores

Center Overview

Period covered by the report: 5/1/2009 – 4/30/2010
EPA Agreement Number: RD83329301-0
Investigators: Marie Lynn Miranda, Richard Auten, Mike Foster, Alan Gelfand, Sherman James, Martha Keating, Pamela Maxson, Geeta Swamy, Redford Williams
Project Period: Year 3

Objectives of the Southern Center on Environmentally-Driven Disparities in Birth Outcomes (SCEDDBO)

The central mission of the Southern Center on Environmentally-Driven Disparities in Birth Outcomes is to determine how environmental, social, and host factors jointly contribute to health disparities. Specific aims of the Center are:

1. *To develop and operate an interdisciplinary children's health research center with a focus on understanding how biological, physiological, environmental, and social aspects of vulnerability contribute to health disparities;*
2. *To enhance research in children's health at Duke by promoting research interactions among programs in biomedicine, pediatric and obstetric care, environmental health, and the social sciences and establishing an infrastructure to support and extend interdisciplinary research;*
3. *To develop new methodologies for incorporating innovative statistical analysis into children's environmental health research and policy practice, with a particular emphasis on spatial, genetic and proteomic analysis;*
4. *To serve as a technical and educational resource to the local community, region, the nation, and to international agencies in the area of children's health and health disparities*; *and,*
5. *To translate the results of the Center into direct interventions in clinical care and practice*.

SCEDDBO leverages and promotes active partnerships among the Nicholas School of the Environment, the Duke University Medical Center, Trinity College of Arts and Sciences, and Duke's Children's Environmental Health Initiative, as well as the Durham County Health Department (DCHD), and the Lincoln Community Health Center (LCHC. The Center brings together the expertise of obstetricians, pediatricians, genetic epidemiologists, spatial statisticians, environmental scientists, social epidemiologists, social psychologists, geographers, and community organizations. SCEDDBO capitalizes on substantial ongoing commitments by Duke University to foster strong interdisciplinary research programs in environmental health sciences.

Synthesis across SCEDDBO. **Research Project A: Mapping Disparities in Birth Outcomes** provides population-level research on health disparities in birth outcomes. Spatially-linking 1.7 million birth records with environmental, social, and host factor data layers allows for population-level analysis of potential co-factors identified in both the clinical obstetrics **Research Project B: Healthy Pregnancy, Healthy Baby: Studying Racial Disparities in**

Birth Outcomes and mouse model **Research Project C: Perinatal Environmental Exposure Disparity and Neonatal Respiratory Health** studies. The data from Research Project A is spatially linked in GIS to the data from Research Project B.

The neighborhood assessment undertaken in Research Project B provides important neighborhood level environmental and social data to Research Project A. In addition, the environmental data developed for Research Project A works synergistically with the mouse model work in Research Project C. For example, the air quality data from Research Project A is being used to further refine experimental dose design in Research Project C. In turn, results from Research Project C regarding experimental effects of multiple environmental agents on fetal growth restriction and postnatal somatic and lung development help point to locations in North Carolina where we look more closely at air quality impacts on birth outcomes in Research Project A.

Thus Research Project A is an epidemiological study, while Research Project B is a complementary clinical obstetrics project. Both projects focus on how combined environmental, social, and host factors shape disparities in birth outcomes. Research Project B also allows for additional host factor analysis. Research Project C uses a mouse model system to explore how disparities in exposure and response to exposure initiate and/or enhance disparities in birth outcomes and subsequent neonatal respiratory health. Like Research Projects A and B, Project C explores the effects of *combined* environmental exposures to prototypical air pollutants common in North Carolina (particulate matter and ozone), as well as genetic background, on fetal growth restriction, neonatal somatic growth, and subsequent lung development and function.

The synergy among the research projects is facilitated by the GIS and Statistical Analysis (GISSA) Core. The GISSA Core allows for data analysis of the very large amount of data through the use of high-end GIS applications in combination with Bayesian spatial hierarchical modeling and other advanced spatial statistical approaches, thus permitting multi-level analysis. Research Projects A and B both apply a Bayesian spatial hierarchical modeling approach to capture uncertainties in pregnancy outcomes and to elucidate the contributions of economic, sociocultural, and environmental stressors on health disparities in fetal growth restriction. State-of-the-art GIS methods allow for sophisticated spatial statistical analyses at highly resolved spatial scales.

The GISSA Core also provides the analysis of the biological response and genetic data generated in Research Projects B and C. The rich source of social, environmental, and host data in Project B, coupled with sophisticated statistical genetic approaches for identifying gene-gene and gene-environment interactions, provides the opportunity to make important discoveries of how these higher order interactions may be working together to promote or prevent adverse birth outcomes. By serving as a central clearinghouse for statistical analysis, the GISSA Core tracks outcomes in each project and uses these discoveries to guide the analysis in each of the other projects.

The Community and Outreach Translation Core facilitates the communication of findings from our large-scale study and future more-focused investigations. The COTC supported the implementation of the neighborhood assessment undertaken in Research Project B and has helped to communicate the results of the assessment to community partners. In addition, the COTC draws on the GISSA Core to develop materials that communicate the results of the research projects in formats and applications that are immediately accessible to the lay public.

SCEDDBO is characterized by significant synergies among center components. To provide concrete examples of how the work of the center is moving forward in a collaborative way, here we highlight four areas: air pollution, social context of environmental stress, the Community Assessment Project, and statistical methods development. We provide summaries in this center overview; additional details can be found in the individual center component write-ups.

Air Pollution. To investigate the relationship of air pollution exposure and pregnancy outcomes, we have examined air pollution in all three projects. In Projects A and B, we have used criteria air pollutant data from the EPA AQS monitoring network, as well as CMAQ and FUSED modeling data. In addition, we have recently obtained highly resolved air toxics data. These data have been spatially linked to the births in both Projects A and B. In addition, we have created a road proximity measure which can be used in both Projects A and B. The road proximity measures allow us to consider a relatively simple metric for assessing risk of exposure to air pollution, specifically traffic-related air pollution which includes particulate matter and diesel exhaust, both of which are being investigated within Project C. We have already published several manuscripts on the relationship between air pollution and pregnancy outcomes and anticipate several more in Years 4 and 5. We are also preparing a manuscript that synthesizes the air pollution work done across projects to be submitted during year 4.

The Social Context of Environmental Stress. We continue to work towards synthesis across all three projects. We have been able to combine our knowledge of the women in Project A with our rich data from the women on Project B. With our access to the North Carolina Detailed Birth Record (DBR) in Project A, we have been able to link participants in Project B with their birth certificate data. Using maternal and infant identifying information, including name, place, and date of birth, we have been able to link 991 (99.9%) participants who completed the study and had a live birth by December 31, 2008 and 59 (76.6%) participants that were lost-to-follow-up but with an expected delivery date on or before December 31, 2008. This linkage will allow us to examine multiple questions including racial residential segregation, residential mobility, and maternal medical complications.

Additionally, the effects of resource deprivation suggested by findings in Projects A and B prompted Project C to add a resource deprivation (nesting restriction) component in order to test the proof-of-principle that the combination of multiple stressors/environmental contaminants may affect health even when the individual exposures do not.

Community Assessment Project/Built Environment. An important measure of potential environmental stress is the built environment. Our Community Assessment Project assessed built environment variables for over 17,000 tax parcels, including the home addresses of over 40% of the participants in the Healthy Pregnancy, Healthy Baby Study (SCEDDBO Project B). Analyses of the built environment data are underway. Seven scales (housing damage, property disorder, security measures, tenure, vacancy, violent crime and nuisances) have been constructed at five levels of geography (census block, primary adjacency neighborhood, census block group, census tract, and city-defined neighborhoods). The continuous and categorical scale variables have been merged with the Durham birth records (Project A) and with the clinical OB women's records (Project B), which enables multiple analyses of the relationships among the built environment, psychosocial health, and pregnancy outcomes. A symposium proposal which would combine the efforts of Projects A and B is in submission for 2011 Society for Epidemiologic Research entitled "The Joint Impacts of Social and Built Environments: Modeling Psychosocial Mechanisms to Health."

Statistical Methods Development. We are pursuing three projects that capitalize on combining information in the data for Project A and Project B. The first project is to utilize the fine detail in Project B data to improve analyses involving Project A data. In particular, the Project A data do not contain information on whether pre-term births are medically indicated or spontaneous. It is conceivable that relationships found in Project A analyses, such as the association of air pollution levels with adverse birth outcomes, could differ when births are medically indicated versus spontaneous. Fortunately, the Project B data does have an indicator for medically-indicated versus spontaneous pre-term birth. We are building imputation models that predict this indicator from correlates available in both datasets. We then impute the missing indicators in the Project A data, thereby enabling us to perform analyses for both types of pre-term births. Basically, we estimate a logistic regression model—using flexible model fitting strategies to ensure accurate predictions—and use that model to impute the missing indicators in Project A data. The resulting imputed datasets can be analyzed by many members of the team.

The second project is to use the Project B data to check the sensitivity of conclusions from Project A analyses to potential unmeasured confounding. Roughly, we test some model from Project A by fitting it on the Project B data, including relevant variables from Project B that were not available in Project A. If the association found in the Project A model remains robust after including the potential confounders from Project B, our confidence in the conclusions increases. We are working on methods that perform such tests in a principled, model-based manner. In a related project, we also are checking the sensitivity of conclusions from Project A analyses to possible measurement errors in the data. For example, highest attained educations for mothers in the intersection of Project A and Project B are quite different on the two files. We treat Project B education values as truth—since we are more confident in their accuracy—and replace the Project A education values with this new truth. For mothers in the intersection of the datasets, we then can re-run analyses to see if results change dramatically. We also are working on imputing corrected values of education for the entire Project A data.

The third project is to explore factors that affect maternal blood pressure during pregnancy. This project involves combining pollution data from Project A with other data from Project B. We consider a variety of statistical approaches for this project, including latent trajectory and sparse functional data models. In the latter approach, we introduce a low-dimensional set of latent factors to predict blood pressure curves. Environmental, social, and genetic factors are used to help explain variation in the blood pressure trajectories. Our ultimate goal is to link these predicted trajectories to birth outcomes; for example, women with monotonically-increasing blood pressure trajectories may exhibit poorer birth outcomes than women with U-shaped curves. Methodological extensions include joint modeling of blood pressure and air pollution trajectories via structural equation models.

Administrative Core

Period covered by the report: 5/1/2009 – 4/30/2010
EPA Agreement Number: RD83329301-0
Investigators: Marie Lynn Miranda, Richard Auten, Sherman James, Pamela Maxson
Project Period: Year 3

Objectives of Core

The Southern Center on Environmentally-Driven Disparities in Birth Outcomes (SCEDDBO) is governed through an Administrative Core that includes an Executive Committee composed of the Director, the two Co-Directors, and the Project Manager; an Internal Steering Committee composed of members of the Executive Committee and the Directors of the Research Projects and the Facility and Community Outreach Cores; and an External Advisory Committee composed of senior environmental health scientists, as well as community representatives, with expertise relevant to SCEDDBO, who provide informal consultation, as well as annual formal evaluation of Center research and outreach activities.

The specific aims of the Administrative Core are to:

a. Provide scientific direction and leadership;
b. Coordinate and foster interactions among research project and facility core investigators;
c. Provide administrative services for the Center;
d. Direct the Young Investigators program; and
e. Represent Duke's SCEDDBO to the university, the community, the NIH, other Children's Environmental Health Centers across the United States, and the policy and scientific community interested in children's environmental health more broadly.

In all activities, SCEDDBO emphasizes the importance of diversity. The decision to focus on health disparities, the gender and racial diversity of Center leadership, the incorporation of natural, social, and biomedical scientists, a commitment to community-based participatory research, and efforts to promote the careers of promising new investigators are all indicative of the importance that we place on fostering environments where all people can prosper.

Progress Report/Summary of Accomplishments

Quality Management Plan. The Administrative Core continued to distribute the Quality Management Plan (QMP) to all new SCEDDBO collaborators. These individuals are required to sign the cover sheet thereby agreeing to abide by the policies laid out in the QMP. The Administrative Core keeps a copy of these signed forms in its files. In addition, the Administrative Core performed an internal audit on the first 1000 participant datafiles for Project B: Healthy Pregnancy, Healthy Baby Study for quality assurance purposes.

Young Investigators Program. Richard Auten and Marie Lynn Miranda continue to mentor Geeta Swamy. Professor Christina Gibson-Davis's research interests evolved substantially since SCEDDBO was awarded funding. As a result, she asked to be relieved of her responsibilities on the SCEDDBO project. With the newly available financial resources, we brought Dr. Heather Stapleton more fully into SCEDDBO. Marie Lynn Miranda serves as Dr. Stapleton's mentor.

Year Three Expenditures. Year three expenditures matched projections in most areas. Spending on lab costs, particularly environmental and genetic analysis, was higher than anticipated, largely due to increased external costs such as the admixture chip and increased participant capture. We used discretionary dollars from the Administrative Core to cover some of these costs from Research Project B.

IRB Certification. A centralized database on IRB and IACUC certification and continuing education requirements is maintained through the Administrative Core. Twice a year, Dr. Pamela Maxson, the QA Manager, verifies that all researchers associated with SCEDDBO have completed their basic certification and continuing education requirements (one credit of continuing education is required each year to maintain certification). Reminders are sent to investigators when they are due for additional training. In addition, Dr. Maxson is responsible for ensuring IRB and IACUC Protocols are renewed and updated as necessary. All of these documents are posted to the SCEDDBO internal website, and paper copies are centrally maintained by Dr. Maxson.

Meetings. The Executive Committee typically met monthly, in advance of the Internal Steering Committee meetings, in order to set the agenda for the larger monthly all-hands meetings. We held our Scientific Advisory Committee (SAC) meeting in December, 2009. With the help of the SAC, we focused on deepening synergies across the three core projects, as well as further enhancing our productivity. In addition, we discussed how best to position SCEDDBO for renewal.

Website. The Administrative Core provided material on SCEDDBO to the EPA for uploading to the EPA children's centers website. In addition, we updated our SCEDDBO website, linked off the website for the Children's Environmental Health Initiative (www.nicholas.duke.edu/cehi). We continue to use our secure internal website that allows for discussion boards, email communication, and document storage associated with the work of each of the SCEDDBO components.

Dissemination. Dr. Miranda represented the scientific mission of SCEDDBO as part of the GEI Exposure Biology Program in August, 2009. Specifically, Dr. Miranda presented a talk entitled "Combining Population Clinical, and Animal Models to Assess Exposure and Effects." Dr. Miranda also presented a talk at the USEPA's "Strengthening Environmental Justice Research and Decision-Making" conference. This talk was entitled, "Using GIS to Support EJ Results" and represented the broad work of the Children's Environmental Health Initiative, including work done under the auspices of SCEDDBO. In addition, numerous talks were given by SCEDDBO investigators at a variety of different conferences as described in the research project write-ups below.

Training opportunities. We provided multiple training opportunities to SCEDDBO investigators and research staff. These opportunities included both intensive short course and semester long coursework for several research staff, as well as travel to professional meetings for researchers supported on the SCEDDBO grant. We also offered training workshops through our Community Outreach and Translation Core, with administrative support provided through the Administrative Core.

New Collaborations. As part of our mission to both support the work of young investigators and advance the research mission of SCEDDBO, we continue our collaborations with Dr. Staci Bilbo, Assistant Professor, Department of Psychology and Neuroscience, Duke University and Dr. Rebecca Fry, Assistant Professor, Gillings Global School of Public Health, UNC. We

continue working with Dr. Bilbo on mouse models to explore the joint impact of environmental and social stressors on birth and developmental outcomes. We are working with Dr. Fry to explore gene expression and epigenetic changes associated with *in utero* metals exposures, with a particular emphasis on cadmium. We have submitted grant applications to NIH and the EPA. In addition, we continue our CDC-funded collaboration with Dr. Heather Stapleton, Assistant Professor, Nicholas School of the Environment, Duke University. This study leverages our ongoing clinical obstetrics project to assess *in utero* exposures to brominated flame retardants, as well as the relationship between brominated flame retardant body burden and maternal thyroid function. We anticipate completing data collection for this collaboration in year 4. We have also written grant applications to the NIH to support further development of this work.

National Service. Duke agreed to host the Children's Environmental Health Centers' monthly conference calls. In addition, Dr. Miranda now serves as a standing member of the Children's Health Protection Advisory Committee. Dr. Miranda also serves as a chartered member of the NIH's Infectious Diseases, Reproductive Health, Asthma and Pulmonary Conditions (IRAP) Study Section. Multiple SCEDDBO investigators help to review proposals for federal funding agencies, as well as review manuscripts for peer-reviewed journals.

Research Project A: Mapping Disparities in Birth Outcomes

Period covered by the report: 5/1/2009 – 4/30/2010
EPA Agreement Number: RD83329301-0
Investigators: Marie Lynn Miranda (PI), Alan Gelfand, Sherman James, Pamela Maxson, Geeta Swamy
Project Period: Year 3

Objectives of Research

Project A's central objective is to determine whether and to what extent joint exposures to socioeconomic and environmental stressors contribute to racial and ethnic health disparities in fetal growth restriction.

Using a geographically-based nested study design moving from analysis of births for the entire State of North Carolina to six demographically and geographically distinct counties to a single health center and state-of-the-art Geographic Information Systems applications with Bayesian spatial hierarchical modeling and other advanced spatial statistical approaches, the specific aims are to:

1. Spatially link detailed birth record, fetal death certificates, socioeconomic, environmental, tax assessor, community-based, and clinical obstetric data at highly resolved scales for the State of North Carolina from 1990-2003;
2. Refine the concept of fetal growth restriction by a) developing a joint distribution for birthweight and gestation using bivariate modeling for live births and fetal deaths – both separately and jointly, and b) defining it in terms of fetal and infant mortality, rather than percentile cut points; and

3. Determine whether and to what extent differential exposures to both environmental and social stressors help explain health disparities in fetal growth restriction among a) African-American women compared to Non-Hispanic white and Hispanic women, b) Older African-American women compared to younger African-American women, c) Hispanic women compared to Non-Hispanic white and African-American women, and d) Foreign born Hispanic women compared to US born Hispanic women.

This project evaluates a large number of factors in diverse populations, providing broad relevance for birth outcomes across time, space, and demography. Identifying social and environmental factors contributing to fetal growth restriction will improve our understanding of disease etiology and explain the racial disparity in disease incidence, leading to effective interventions against poor outcomes in all population groups. Of note, we have expanded our inquiry beyond fetal growth restriction to encompass a broader range of pregnancy outcomes.

Progress Report/Summary of Accomplishments

Over the past year, the Project A research team has met both at full group level and in small groups to discuss new research ideas, review progress of current analysis, and identify next steps, and work on manuscript preparation.

Air Pollution. We have spent considerable time linking the detailed birth record data to USEPA PM_{10}, $PM_{2.5}$, and ozone monitoring data in order to study the impact of *maternal exposure to air pollution* on birthweight. Initial work built customary regression models to assess the linkage and has been published in the *Journal of Exposure Science, Environment, and Epidemiology*. We are especially focused on refining exposure metrics to most effectively characterize meaningful exposures, as well as to capture any windows of vulnerability. Spatial and non-spatial hierarchical models have been explored, incorporating uncertainty in exposure as a function of distance from nearest monitoring station. An associated manuscript is currently in submission.

Related work has studied the use of a $PM_{2.5}$ exposure simulator to explain birthweight. In a recently submitted paper, a template is developed for using an *environmental dose simulator* to connect ambient exposure to personal exposure. Then, using various exposure metrics, calculated from these personal exposures that are clinically plausible over the course of a pregnancy, linkage is built to adverse birth outcomes. This work is forthcoming in *Environmetrics*.

In an extension of our previous work linking air quality monitoring data for PM_{10} and $PM_{2.5}$ with the detailed birth record, we have been working on an analysis of the relationship between maternal exposure to particulate matter during pregnancy and the occurrence of pregnancy-induced hypertension. We have found that among women living within 20km of a monitor, higher levels of pregnancy-averaged PM_{10} and $PM_{2.5}$ were associated with an increased risk of pregnancy-induced hypertension. This work, for which we are collaborating with investigators at the EPA, was presented at the Society for Epidemiologic Research in June 2010 and a manuscript is currently in preparation. In Year 4, we plan to extend this work to other criteria air pollutants and to include additional adverse birth outcomes.

As part of our larger efforts exploring the relationship of air pollution exposure and pregnancy outcomes, we sought to consider a relatively simple metric for assessing risk of exposure to air pollution, specifically traffic-related air pollution which includes particulate matter and diesel exhaust, both of which are being investigated within Project C. We utilized the statewide GIS

layer of street-geocoded 2005-2007 births to calculate the proximity of each geocoded birth to the nearest primary and secondary roadway. While controlling for all standard covariates, we incorporated measures of air pollution exposure as dichotomous variables indicating residence within 500, 250, 150, 100, or 50m of a primary or secondary roadway into models for birthweight, LBW, VLBW, PTB, VPTB, and any hypertensive disorder. Our findings, which are presented in a manuscript that will be submitted in the coming year, indicate a significant dose-response relationship between proximity to a primary or secondary road and the adverse outcomes of PTB, VPTB and hypertension—for example, the probability of hypertension is increased by living within 500m of a primary or secondary roadway, with this probability being even higher at 250m, and still higher at each of 150, 100, and 50m.

Work continues on building *spatial downscalers*. Such modeling strategies enable the fusion of monitoring station data with computer model output to better assess environmental exposure. Then, we can utilize improved exposure assessment to examine linkage between exposure and adverse birth outcomes. A first paper on univariate exposure has been accepted at the *Journal of Agriculture, Biological and Environmental Statistics*. A follow-on paper considers downscaling for co-pollutants and reveals the benefits of studying exposures jointly. This work is forthcoming in the *Annals of Applied Statistics*. Recognizing the potential for "modeling" error in computer model output, we are completing a third manuscript which enables local directionality in spatial structure to recalibrate the model output as well as to improve the fusion with station data.

Racial Residential Segregation. Our project on *racial residential segregation* has now seen the near completion of one paper (currently in preparation) which enables quantification of racial exposure/isolation at finer spatial scales within SMSA's. Such a measure can be connected to measures of social and economic disadvantage at these scales to gain insight into how racial residential segregation has manifested itself across urban landscapes. In turn, this promises to reveal key insights into how to think about the spatial aspects of the social factors influencing health disparities. We are working to determine which facets of segregation best characterize the way community-level racial residential segregation acts to promote health disparities in birth outcomes. Although our initial efforts were statewide, we have since decided that, given the significantly more detailed data available for Durham County, we will focus on this area while we work to determine what variables are most important to characterizing racial residential segregation in terms of its health consequences.

Nulliparous Women. In Year 3 we submitted a manuscript describing analysis exploring the observed association between parity and risk of adverse birth outcomes (i.e. women having their first child are increased risk of adverse outcomes compared to women who have already had at least one child). We linked births in the North Carolina Detailed Birth Record 1990-2007 with previous and subsequent births to the same mother using deterministic techniques that evaluated various combinations of maternal identifying variables to link births, including full name, maiden name, date and state of birth, parity, and date of last birth. We employed statistical and modeling-based analyses to estimate first birth outcome rate differences between nulliparas who did have a subsequent pregnancy versus those who did not. Among nulliparas that were not linked to a second birth, maternal-age-adjusted rates of multiple measures of adverse outcomes, including maternal medical complications, were almost all statistically higher compared to rates for linked women. This work suggests that the observed differences in rates of adverse outcomes between nulliparas and multiparas are partly attributable to higher risk women not having a subsequent pregnancy (either by choice or due to fecundity differences).

Community Assessment Project/Built Environment. Analyses of the built environment data are underway. Seven scales (housing damage, property disorder, security measures, tenure, vacancy, violent crime and nuisances) have been constructed at five levels of geography (census block, primary adjacency neighborhood, census block group, census tract and city-defined neighborhoods). The continuous and categorical scale variables have been merged with the Durham birth records. A comparison of the results obtained from models comparing the relationship between the built environment scales and preterm birth at two distinct units of aggregation (the city-defined neighborhoods and census block groups) will be presented at the Society for Epidemiologic Research in June 2010. This work will be expanded to consider all five units of aggregation early in year 4. Using the built environment scales constructed at the primary adjacency neighborhood unit, a paper assessing the associations between these scales and five birth outcomes (preterm birth, low birth weight, small for gestational age, continuous birth weight and birth weight percentage for gestational age) has been drafted. It will be submitted early in year 4.

Seasonality. We have examined the relationship between seasonality and pregnancy outcomes. Our initial aspatial models indicated that the effect of season was most apparent among non-Hispanic white women. We are currently working on spatial models to better understand what factors of season of conception or birth are influencing pregnancy outcomes.

Environmental Contributions to Disparities in Pregnancy Outcomes. We published a review article on social and environmental contributors to disparities in birth outcomes based on both national and North Carolina data, as a way of compiling the many literatures we have accessed throughout our work on Project A. The manuscript, published in *Epidemiologic Reviews*, reviews research on how environmental exposures affect pregnancy outcomes and how these exposures may be embedded within a context of significant social and host factor stress.

Racial Disparities in Maternal Hypertensive Disorders. We analyzed data from North Carolina to determine how the pattern of maternal hypertensive disorders differs among non-Hispanic white, non-Hispanic black, and Hispanic women across the range of maternal ages. In addition we explored whether rates of poor birth outcomes, including low birth-weight and preterm birth, among hypertensive women differed by race. This manuscript is forthcoming in *Public Health Reports* in 2010.

Maternal Age and Birth Order. Investigations of maternal age, birth order, and birthweight have not delineated the relative contributions of each factor to birthweight, especially as they may differ by race. Using the NC DBR data from 1999-2003, we modeled maternal age and birth order on birthweight, adjusting for infant sex, education, marital status, and race. Birth order exerts greater influence on birthweight than maternal age, with significantly different effects across racial subgroups. A manuscript on this work is in submission.

Statistical Methods Development. Out of efforts to develop new spatial methodologies for addressing health disparities, additional methodological work on *disaggregated spatial modeling for areal unit categorical data* went forward. This work uses innovative statistical methodology that extends spatial disease mapping techniques to model subgroups within areal units using a spatially smoothed, multilevel loglinear model. This work appeared in the *Journal of the Royal Statistical Society, Series C*. An attractive feature of this methodology for public health applications is the possibility to elucidate health disparities across space, across subgroups, and space-subgroup interactions.

Bivariate Normal Mixture Models. Another completed manuscript builds *joint models for birthweight and gestational age* using bivariate normal mixtures. Such joint modeling adjusts for maternal risk factors and provides mixture analysis of the residuals to help illuminate further subpopulations with differential risk for adverse joint birth outcomes. It also avoids potential causal inference issues. Modeling of the mixture components is done through gestational age and then birthweight given gestational age. This work is forthcoming in *Statistics and Medicine*. There is continuing work on this project. Our initial effort was non-spatial, ignoring the geo-coded locations of the births. It was also atemporal, ignoring the year of the birth, and it addresses only individual level risk factors but no environmental risk factors. Also, all of this work was confined to finite bivariate normal mixture models. Through the use of Dirichlet process mixed models, we can allow the data to inform regarding the number of mixture components, as well as associated clustering of births.

Spatial Quantile Regression. Novel work on spatial quantile regression has made substantial progress. We want to understand how dependence of response (birth weight) varies with quantile. Does the regression on median or mean birthweight look different from that for the 0.1 quantile? This is important given the greater interest in explaining low birthweight rather than in explaining average birthweight. Also, we expect quantile regressions to be more similar to each other when they are closer spatially than when they are farther apart. This requires the development of spatial quantile processes. Two manuscripts are in development summarizing this work.

Flexible Bayesian Spatial Discrete-time Survival Model. In addition, we have developed a flexible Bayesian spatial discrete-time survival model to estimate the effect of environmental exposure on the risk of preterm birth. We view gestational age as time-to-event data where each pregnancy enters the risk set at a pre-specified time (e.g. the 32th week). The pregnancy is then followed until either (1) a birth occurs before the 37th week (preterm); or (2) it reaches the 37th week and a full-term birth is expected. As preliminary analysis, the methodology was applied to a dataset of geo-coded births in North Carolina in 2002. We estimated the risk of preterm birth associated with short-term exposure to fine particulate matter using air quality metrics derived from the EPA's Statistically Fused Air Pollution Database. We also conducted a simulation study and compared the proposed approach to the standard case-control and time series design. Two associated manuscripts are in preparation.

Statistical Methods for Multivariate Spatial Data Measured on Different Scales. We are currently developing multivariate spatial models for birth outcomes measured on different quantitative scales. These outcomes include continuous variables, such as birthweight and gestational age; categorical variables, such as preterm birth and small for gestational age (SGA); and zero-inflated count variables, such as occurrences of medical complications. The multivariate approach allows us to explore geographic variation among several variables at once, rather than focusing on one variable at a time. Moreover, by taking into account the correlation between various outcomes, multivariate models improve the precision of regression estimates and the ability to detect exposure effects. As part of our analysis, we are considering a variety of multivariate conditionally autoregressive (CAR) models, including multivariate intrinsic CAR models, multivariate proper CAR models, finite mixtures of CAR models, and Dirichlet process CAR models. This last approach accommodates uncertainty in the underlying CAR specification for the spatial random effects. In Year 4, we plan to apply these models to the Detailed Birth Record (DBR) data, as part of an ongoing effort to examine ways in which environmental, host, and psychosocial factors affect birth outcomes across different regions of North Carolina.

Collaborations with other SCEDDBO Components

We have worked closely with the Project C investigators to design analysis looking at the same pollutants at comparative levels of exposure from different methodological perspectives. Our discussions with the investigators of Project C help inform our methods for framing ozone and particulate matter exposures in our models, as well as help refine the planning and implementation of future animal models in Project C. As the dataset being collected under Project B reaches a size and completeness suitable for analysis, we plan to bring some of the methodological strategies developed under Project A to this dataset including synthesis with the Detailed Birth Record data, the mixture modeling for birthweight and gestational age, and the refined environmental exposure approaches. Arguably, synthesizing the DBR data with the clinical OB database is our biggest challenge. We understand the issues here - the clinical OB births are contained in the DBR births but are not sampled randomly; the clinical OB dataset is much more complete but, due to the biased sampling of this dataset, relationships within this dataset (joint probabilities of events) will not necessarily extrapolate to the DBR data. However, with knowledge regarding the nature of the bias in recruitment for the clinical OB dataset, we will attempt to revise these joint probabilities to be applicable to the DBR data. This effort extends across both Projects A and B.

Meanwhile, we have begun examining residential mobility by linking women who are in both Projects A and B. This linkage will allow us to determine who is moving during pregnancy (by comparing the address at enrollment and the DBR address at delivery) and the nature of those moves, including the quality of the new location compared to the previous location (and thus changes in environment or exposure).

Future Activities

We plan to continue working on each of the areas described in the progress report/summary of accomplishments section. Achieving a better understanding of exposure to air toxins, as well as particulate matter and ozone, is a central focus of our future efforts. Areas of investigation will include space time analysis of trends in births across North Carolina, an investigation of linked births (same mother) using suitable random effects models, and a more thorough investigation of the impact of introducing spatial random effects in regression modeling to explain birth outcomes.

Community assessment/built environment. We plan on continuing our analyses in year 4 to further explore the impact of the built environment on birth outcomes and to examine associations between the built environment and racial residential segregation.

Residential Mobility. As indicated above, we recently began the process of linking participants in Project B with their associated birth certificate record. We are excited to begin exploring the additional insights into the detailed birth record data that can be gleaned by linking these data with the rich dataset collected in Project B. This linkage will not only allow us to explore issues of data accuracy in the detailed birth record, but will also allow us to begin implementing the methods of synthesizing categorical data discussed above.

Survival Approach with Air Pollution and Preterm Birth. We plan to examine the risks of preterm birth due to long-term and short-term exposures to ambient fine particulate matter and its chemical constituents. We will apply the survival approach to geo-coded births in North Carolina for the period 2001 to 2005 separately for each county. County-specific risks will be combined via a two-stage Bayesian hierarchical model where effect modification due to county characteristics will also be explored. Moreover, we plan to extend the analysis to (1) account for

exposure measurement error, (2) differentiate spontaneous and medically indicated preterm births, and (3) jointly model gestational age and birth weight.

Spatial Analysis. We have made one of our primary objectives for year 4 the development of spatial analogue models for each of the non-spatial analyses we carry out. The motivation for this is to test whether parameter estimates derived from non-spatial models are biased due to spatial autocorrelation in standard regression model error terms. Spatial analysis will account for unobserved characteristics related to the study outcome that may be spatially patterned.

The specific spatial model, known as the Conditional Autoregressive (CAR) model, that has been our focus assumes that study outcomes in neighborhoods that share a boundary with each other are not spatially independent. In effect, we are able to estimate a spatial random effect associated with each neighborhood unit, where the value of this effect is equal to the mean value over adjacent areal units. Estimation also provides us with a spatial variance, which speaks to overall variability in the outcome across the study region. This spatial approach not only has the potential to improve parameter estimates but also allows us to identify areas with increased risk of a poor outcome.

We are currently developing a spatial model that mimics our seasonality analysis and have plans to do the same for other non-spatial analyses currently underway.

*Racial Residential Segregation. S*everal analyses are planned for year 4 including: (1) determining whether the effect of neighborhood level racial isolation on birth outcomes varies by the geographic scale used to proxy a neighborhood unit; (2) investigating whether the racial isolation effect varies by maternal SES factors such as education level and marital status; (3) extending the black – black isolation and white-white isolation analyses to a multiple county analysis, in order to examine the robustness of the association across study areas; and (4) determining whether neighborhood scale racial isolation relates to maternal level psychosocial factors (e.g., depression and other mental well-being indicators), which may then in turn impact birth outcomes.

Dissemination. We continue to target various professional audiences for dissemination of our work. Recent presentations have been at conferences under the auspices of the Joint Statistical Meetings, the American Public Health Association, the Society of Epidemiological Research, the International Biometric Society, and the Society of Maternal and Fetal Medicine.

Publications – Accepted

Berrocal, V, Gelfand, A, Holland, D. A Spatio-temporal Downscaler for Output from Numerical Models. J*ournal of Agricultural Biological and Environmental Sciences,2009.*

Berrocal, V, Burke, JM, Gelfand, A, Holland, D, and Miranda, ML. On the Use of a $PM_{2.5}$ Simulator to Explain Eirthweight. Forthcoming, *Environmetrics*.

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Gray, S, Edwards, S, and Miranda, ML. Assessing Exposure Metrics for PM and Birthweight Models. *Journal of Exposure Science and Environmental Epidemiology, 2010, 20(5),* 469-477.

Schwartz, S., Miranda, ML., Gelfand, A. Joint Bayesian Analysis of Birthweight and Censored Gestational Age Using Finite Mixture Models. *Statistics in Medicine, 2010, 29 (16),* 1710-1723.

Tassone, E, Miranda, ML, Gelfand, A. Disaggregated Spatial modeling for Areal Unit Categorical Data. *Journal of the Royal Statistical Society,* 2010*, 59,* 175-190.

Publications – In Preparation/Submission

Anthopolos, R, James, SA., Gelfand, A., Miranda, ML. A Spatial Measure of Neighborhood Scale of Racial Isolation Applied to Low Birthweight in North Carolina. In submission.

Finley, A., Banarjee, S., Gelfand, A., Miranda, ML. Approximately Optimal Spatial Design for Categorical Response Data. In preparation.

Lum, K., Gelfand, A., Miranda, ML. Spatial Quantile Regression Modeling using Asymmetric Laplace Processes with Application to Birth Outcome Data. In preparation.

Miranda, ML., Edwards, S., Meyers, E. Adverse Birth Outcomes among Nulliparas Versus Multiparas. In preparation.

Swamy, G., Edwards, S., Miranda, ML., Gelfand, A., James, SA. Maternal Age, Birth Order, and Race: Differential Effects on Birthweight. Resubmitted.

Miranda, ML, Maxson, P, Edwards, S, Swamy, GK, Gelfand, A, James, SA. Disparities in Maternal Hypertension and Pregnancy Outcomes: Evidence from North Carolina, 1994-2003. In submission.

Miranda, ML, Maxson, P, Kim DK. Early Childhood Lead Exposure and Exceptionality Designations for Students. In submission.

Presentations

Anthopolos, R., James, SA., Gelfand, A., Berrocal, V., Miranda, ML. A Neighborhood and Spatial Measure of Racial Isolation Applied to Birthweight. American Public Health Association, Philadelphia, November, 2009.

Anthopolos, R, James, SA., Gelfand, A, Miranda, ML. A Neighborhood Level Spatial Measure of Racial Residential Isolation for Health Disparities Research. Society for Epidemiologic Research, Anaheim, June, 2009.

Gray, S., Gelfand, A., Miranda, ML. Adjusting for Measurement Error in Maternal PM Exposure and Birth Weight. Eastern North American Region, New Orleans, March 2010.

Gray, S., Edwards, S., Miranda, ML. Assessing Exposure Metrics for Air Pollution and Birthweight Models in North Carolina. American Public Health Association, Philadelphia, November, 2009.

Gray, S., Edwards, S., Miranda, ML. The Effect of PM Exposure on Birthweight. Society for Epidemiologic Research, Anaheim, June, 2009.

Miranda, ML., Maxson, P., Kim, D. Early Childhood Lead Exposure and Exceptionality Designations for Students. American Public Health Association, Philadelphia, November, 2009.

Supplemental Keywords
Data fusion, meta analysis, disparities, spatial disaggregation, spatial interpolation, spatial modeling, racial residential segregation

Research Project B: Healthy Pregnancy, Healthy Baby: Studying Racial Disparities in Birth Outcomes

Period covered by the report: 5/1/2009 – 4/30/2010
EPA Agreement Number: RD83329301-0
Investigators: Redford Williams (PI), Allison Ashley-Koch, Richard Auten, , Pamela Maxson, Marie Lynn Miranda, Jerome Reiter, Geeta K. Swamy,
Project Period: Year 2

Objectives of Research

The central objective of the Healthy Pregnancy, Healthy Baby Study is to determine how the interaction of environmental, social, and host factors contributes to disparities in birth outcomes between African-American and white women in the American South. There are four specific aims:

1. Conduct a cohort study of pregnant women in Durham, NC designed to correlate birth weight, gestation, and birth weight x gestation with environmental, social, and host factors;
2. Develop community-level measures of environmental and social factors by inventorying neighborhood quality and the built environment in partnership with local community groups;
3. Create a comprehensive data architecture, spatially resolved at the tax parcel level, of environmental, social, and host factors affecting pregnant women by linking data from the cohort study and neighborhood assessments with additional environmental and socioeconomic data; and
4. Determine whether and to what extent differential exposures explain health disparities in birth outcomes by applying innovative spatial and genetic statistical methods to:
    a. Identify environmental, social, and host factors that cluster to predict birth outcomes in the entire sample,
    b. Determine whether these clusters are more or less present in African-American versus white populations and quantify the proportion of health disparities explained by differences in cluster frequency, and
    c. Identify environmental, social, and host factors that cluster to predict birth outcomes within the African-American and white sub-samples and compare these clusters across racial groups.

Progress Report/Summary of Accomplishments

As of 4/30/10, 1738 women have been enrolled in the study. Women are recruited from Duke University Medical Center (DUMC) and the Durham County Health Department's prenatal clinic at Lincoln Community Health Center. Demographic data indicate that we are successfully recruiting women who are most at risk for adverse pregnancy outcomes, particularly low-income, low educational attainment, and non-Hispanic black women.

The following information is collected from participants in the Healthy Pregnancy, Healthy Baby Study:

- Psychosocial measures include: CES-D, perceived stress, self-efficacy, interpersonal support, paternal support, perceived racism, perceived community standing, pregnancy intention, John Henryism Active Coping Scale, NEO Five Factor Inventory of personality.
- Environmental exposure survey measures include: short survey on fish consumption, smoking pattern and exposure to second-hand smoke, and drinking water source.
- Maternal and neonatal medical record abstraction includes: detailed pre-pregnancy medical and social history, antepartum complications, birth outcomes, and neonatal complications.
- Blood samples for genetic and environmental analysis to assess candidate genes related to environmental contaminant (nicotine, cotinine, cadmium, lead, mercury, arsenic, and manganese) metabolism, inflammation, vascular dysfunction, and stress response.
- Cord blood and placental samples are currently being stored for future genetic analysis and evaluation of activity at the maternal-fetal interface.

We have been highly successful in collection of participant-level data as well as biological samples, with greater than 90% attainment of maternal blood sample for genetic and environmental analyses. Collection of cord blood and placental samples, which began in June 2007, has also been successful with approximately 763 delivery samples collected.

All maternal data are georeferenced (i.e., linked to the physical address of the mother) using Geographic Information System (GIS) software. The Healthy Pregnancy/Health Baby Study also draws on an in-depth neighborhood assessment designed to capture both built environment and community-level social stressors and community resources. The cohort study and neighborhood assessment data are spatially linked to extensive environmental and demographic data at a highly resolved spatial scale.

To date, we have generated genotypes on 1243 blood samples from pregnant women for 405 Single Nucleotide Polymorphisms (SNPs) in fifty-one genes. Candidate genes include those involving human environmental contaminant clearance (heavy metals and environmental tobacco smoke), infection and inflammation (cytokines, chemokines, and bacterial pathogen recognition), maternal stress response (serotonin), and other pathways that have been implicated as potential drivers of health disparities (vascular responsivity). <u>At this point in the study, we have genotyped nearly every candidate gene we proposed in the application.</u>

In addition to our candidate gene analyses, this past year, we gave considerable thought to the issue of population stratification. Our baseline approach to analysis has always been to consider the non-Hispanic black (NHB) and non-Hispanic white (NHW) women in separate analyses. The bulk of our sample is comprised of NHB women and it is expected that even within that group there is variability in genetic make-up. To address this, we have generated the Illumina African American Admixture Chip on 824 NHB women. This admixture chip contains 1509 SNPs which were specifically selected due to the disparate frequencies in the Yoruban (African) and Caucasian HapMap samples, the two primary ancestral populations of NHB women. These data are currently being used in two ways. The first approach is to use these

data to cluster the NHB women into sub-populations. Membership assignment to sub-populations will be used as a covariate in our future candidate gene studies as a means to further protect against population stratification. The second approach will be to exploit these data to identify regions of the genome that may be over-represented by one of the ancestral populations and also associated with the occurrence of our fetal and maternal outcomes. This admixture mapping approach has been used successfully to map genes for obesity, renal disease, and multiple sclerosis, among others. We view the admixture mapping approach as a hypothesis generating exercise to point us to regions of the genome that otherwise we may not have examined. In this regard, it is very complementary to the candidate gene approach that we have been taking whereby we make hypotheses concerning the involvement of specific candidate genes *a priori* given what we know about the biology of our fetal and maternal outcomes. It is important to note that we have been judicious with our budget and resources in order to afford the Admixture Chips. It was not part of the original proposal, but we felt that it would add significantly to the quality of our analyses and the flexibility of hypotheses examined.

In the coming year, we expect to continue our genotyping efforts. We are already scheduled to run approximately 180 more samples for the Admixture Chip. Our candidate gene genotyping will include both generation of genotypes in recently collected samples for the existing candidate genes, and also prioritizing new candidate genes involved in contaminant metabolism and stress-response.

Statistical analysis regarding candidate gene polymorphisms began in June 2008 and is ongoing. Preliminary genetic analyses are described below.

In our progress report last year, we detailed results from our analyses of the ***Vitamin D receptor gene (VDR)*** gene and infant birth weight. We are pleased to report that this work has been accepted for publication in the *American Journal of Medical Genetics*.

We have also examined polymorphisms in the **G-protein coupled receptor kinase 5** (GRK-5) gene. GRK5 is associated with a pharmacogenomic interaction among African Americans in the setting of cardiovascular disease and response to β-adrenergic receptor (βAR) blockade, which is standard therapy for cardiac failure and ischemia. Because of the association with cardiovascular disease, we hypothesized that GRK-5 genetic variation was associated with hypertensive disorders in pregnancy. We defined hypertensive disorders as chronic hypertension (CHTN=BP>140/90 before 20 wks), preeclampsia (BP>140/90 and proteinuria), and CHTN + superimposed preeclampsia (CHTN with new onset or worsening proteinuria). Haplotype tagging single nucleotide polymorphisms (SNPs) were genotyped for GRK-5 via Taqman assays. Logistic regression was used to examine the relationship between maternal genotype and each hypertensive disorder among the NHB women, adjusting for age, education, insurance, tobacco use, and pre-pregnancy BMI. CHTN was included as a covariate in the model for preeclampsia. In our NHB data set, 125 out of 587 participants (21%) were diagnosed with preeclampsia. Of the 17 SNPs examined, 3 were nominally associated with preeclampsia. For the most significant association with rs10886445 (global p=0.0009), the odds of preeclampsia for NHB women with the CC genotype were 0.28 times that for NHB women with the TT genotype (CI: 0.1429, 0.552). For those NHB women with the CT genotype, the odds of developing preeclampsia were 0.33 times that for NHB women with the TT genotype (CI: 0.1682, 0.656). In addition, rs12416565 (global p=0.003) and rs11198925 (global p=0.02) were also nominally associated. For CHTN, only one marker (rs2420620, global p=0.02) demonstrated nominal association. Similarly, for CHTN+preeclampsia, only one marker (rs10510055, global p=0.02) demonstrated nominal association. Based on these results, we concluded that the GRK-5 gene may play a role in hypertensive disorders of pregnancy,

particularly the development of preeclampsia. Future analyses will examine the effects of GRK-5 on blood pressure regulation (see below our work on defining blood pressure trajectories in our data set) and potential pharmacogenomic interactions during pregnancy. These data were presented earlier this year at the Society for Maternal and Fetal Medicine and are currently being written up as a manuscript to be submitted in the next few months.

We have also begun to examine gene by environment interactions in our data set. We have findings of several gene*environment interactions (G*E) involving exposure to environmental tobacco smoke (ETS) as measured by cadmium and cotinine in the blood of our mothers. In addition, we have begun to focus more acutely on air pollution in these gene*environment interactions using proximity to roadways and road density data.

In our NHB women, we have examined G*E between genes in the inflammatory pathway and ETS as they relate to infant birthweight and identified several nominal associations, the most significant being rs2069771 in the interleukin-2 gene with cadmium exposure (global p=0.005) and rs9005 in the interleukin 1 receptor antagonist with cadmium exposure (global p=0.006). In addition, also among the NHB women, we have identified G*E interactions between the n-acetyltransferase genes and cadmium exposure predicting maternal preeclampsia and infant outcomes. In particular, rs8190845 in NAT1 interacted with cadmium exposure to predict occurrence of preeclampsia in the mother (global p=0.009). Additionally, rs17126345 , also in NAT1, interacted with cotinine exposure to predict the occurrence of preterm birth as defined as delivery prior to 37 weeks gestation (global p=0.006). The analyses of G*E with the inflammatory genes and G*E with the n-acetyltransferase genes are both currently being written for publication. Moreover, these results will also be submitted in abstract form to the annual meeting of the American Society of Human Genetics.

Statistical Methods Development. The project team continued to develop new ways of handling missing data in large epidemiological studies in which interaction effects are suspected. The main approach is to adapt regression trees to perform multiple imputation. This approach is being used to handle the missing data in the prospective study of Project B. This methodology has the potential to be utilized in a wide range of settings, including outside of epidemiological contexts. An article describing this work has been accepted for publication in the *American Journal of Epidemiology.*

The team examined approaches to performing Bayesian analysis after multiple imputation is used for missing data. This work is motivated by the use of the tree methodology for multiple imputation, because we are estimating Bayesian models with the completed datasets (see the paragraph on Bayesian quantile regression with latent factors below). An article describing this research was published in *The American Statistician*.

The team developed methods for exploring sets of important predictors in large epidemiological studies when quantile regression will be used for the outcome variable. These methods adapt penalties from ordinary least squares lasso regression and elastic net regression so that they enable quantile regression. The team is using this methodology to explore the most important predictors of adverse birth outcomes in the prospective study of Project B. A manuscript describing this work is in preparation and will be submitted in fall 2010.

The team developed an approach for performing Bayesian quantile regression with latent factors. The motivation for this development is as follows. Many of the predictors of adverse birth outcomes do not strongly predict adverse birth outcomes, likely because of the modest sample size for the strength of associations seen in the data. However, many of the predictors

can be conceptualized as indicators of underlying factors that could be strong predictors; for example, several of the psychosocial variables can be grouped as a factor indicating the amount of social support available to the mother. We developed and are applying methodology for estimating the effects of these factors on birth outcomes using the prospective study of Project B. A manuscript describing this work is in preparation and will be submitted in fall 2010.

Finally, the team developed an approach for assessing sensitivity to unmeasured confounding when using principal stratification. This work was motivated by the presence of several intermediate variables in the prospective study of Project B, e.g., hypertension as an intermediate variable for gestation age. At this point, this work is at a theoretical stage; we have not yet applied it on Project B data. A manuscript on the theory has been submitted to a peer-reviewed journal.

We wish to examine whether and to what extent environmental exposures are associated differentially between medically indicated and not-medically indicated (spontaneous) preterm births. However, since information on the clinical subtypes of preterm birth is not available from the North Carolina Detailed Birth Record database, we will first develop a prediction model for spontaneous preterm births using data from the prospective study of Research Project B. By treating the indicator of whether a preterm birth was spontaneous as missing, we plan to generate multiple complete datasets for geo-coded preterm births in Research Project A. Statistical analyses will then be conducted under a multiple imputation framework. Moreover, because the recruited participants are not representative of the state-wide birth cohort due to different spatial and temporal domains, we will also explore inference for multiple imputed datasets when the records used for imputation are not used for analysis.

Psychosocial Indicators. Analyses have been completed on psychosocial influences on birth outcomes. The relationships among pregnancy intention, psychosocial health, and pregnancy outcomes have been examined, with a draft paper ready to submit early in year 4. This work was presented at the American Public Health Association annual meeting. In addition, we are examining pregnancy intention, behavioral choice, and environmental exposures. This work will be presented at the Pediatric Academic Society meeting in May, 2010 (year 4). The influences of psychosocial health and smoking status have been studied, and a draft paper will be ready to submit early in year 4. In order to reduce the number of psychosocial variables, cluster analysis has been performed, resulting in three distinct clusters of women. These clusters are being examined in relation to other domains, such as genetics, personality, pregnancy outcomes. This work will be presented at the Society for Epidemiologic Research in June, 2010 (year 4).

Maternal Medical Complications. Fetal health is not only individually determined, but is also influenced by maternal health and well-being. This past year, we have begun to examine maternal outcomes, as well. In particular, we have begun to focus on maternal hypertensive conditions. As a first step, we are trying to identify factors that affect maternal blood pressure during pregnancy. In order to make use of the entirety of blood pressure readings collected across the pregnancy, we are considering a variety of statistical approaches. To address this question, we developed a Bayesian finite mixture model to jointly examine the associations between longitudinal blood pressure trajectories, PTB, and LBW. The model partitions women into distinct groups characterized by an average mean arterial pressure (MAP) trajectory, a probability of PTB, and a probability of LBW. Our approach also introduces a correlated probit model within each cluster to capture residual correlation between PTB and LBW. We recently completed the data analysis, and plan to submit the results to a statistical journal during Year 4. Our ultimate goal is to use environmental, social, and genetic data (such as GRK5 polymorphisms) to predict these blood pressure trajectories. We hope these predicted

trajectories will aid us in predicting birth outcomes; for example, women with monotonically-increasing blood pressure trajectories may exhibit poorer birth outcomes than women with U-shaped curves.

*Environmental Sampling***.** Using the maternal environmental blood samples collected on all participants in Project B, we have been working to characterize maternal exposures to toxics. In addition to documenting the blood lead burdens among a cohort of pregnant women in Durham County, NC, we have been able to characterize current maternal exposures to lead by linking each participant to the tax parcel at which they resided during their pregnancy. We found that both year built and modeled lead exposure risk at participant's residence during pregnancy were not predictive of maternal blood lead levels. Taken in combination with results showing that maternal blood levels increased with age and parity, these findings indicate that maternal blood lead levels are much more likely the result of lead remobilization from historic exposures as opposed to contemporaneous exposures. A manuscript on this work has been published in the *International Journal of Environmental Research and Public Health*.

*Residential mobility***.** With our access to the North Carolina Detailed Birth Record (DBR) in Project A, we have been able to link participants in Project B with their birth certificate data. Using maternal and infant identifying information, including name, place, and date of birth, we have been able to link 991 (99.9%) of participants who completed the study and had a live birth by December 31, 2008 and 59 (76.6%) of participants who were lost-to-follow-up but with an expected delivery date on or before December 31, 2008. This linkage will allow us to determine who is moving during pregnancy (by comparing the address at enrollment and the DBR address at delivery) and the nature of those moves, including the quality of the new location compared to the previous location (and thus changes in environment or exposure).

Roadways. In parallel to the Project A work with road proximity metrics, we geocoded Project B participants to the tax parcel level and then calculated the distance to the nearest roadways. In the coming year, we are planning to run analysis that extends the road proximity work in Project A by incorporating the rich set of variables available in Project B, including analysis looking at how psychosocial health and gene-by-environment interactions may influence the impact of traffic-related air pollution on birth outcomes.

Community Assessment Project/Built Environment. The Community Assessment Project (CAP) assessed built environment variables for over 17,000 tax parcels, including the home addresses of over 40% of the participants in the Healthy Pregnancy, Healthy Baby Study (SCEDDBO Project B). Seven scales (housing damage, property disorder, security measures, tenure, vacancy, violent crime and nuisances) have been constructed at five levels of geography (census block, primary adjacency neighborhood, census block group, census tract and city-defined neighborhoods). Analyses have begun assessing the relationship between the built environment and maternal psychosocial status. A paper assessing the built environment and maternal pregnancy intention among the clinical ob cohort (Project B) is well-underway.

Collaborations with other SCEDDBO Components

The collaborative efforts this year have increased significantly. The entire SCEDDBO team has prioritized air pollution as one of the primary environmental contaminants to be examined across projects. This has involved significant discussions between members of Project B with members in Project A to construct viable markers of air pollution, including proximity to primary and secondary roadways, and NATA data. Project B also prioritized the interleukin/inflammatory genes for analysis after consultation with Project C so that we could support more biological synergies across the two projects. Similarly, Project C introduced a

nest-deprivation model into the ongoing animal experiments in an attempt to better replicate the more complex psycho-social stressors experienced by the mothers in Project B. Linking the North Carolina Detailed Birth Record (DBR) in Project A with participants in Project B will enable us to pursue multiple collaborations between Projects A and B, such as residential mobility and maternal medical complications. The Community Assessment Project/Built Environment data reaches across all three projects. The built environment indices will be used across Projects A and B and will inform Project C regarding its deprivation model. And finally, the statistical team for the GISSA has worked hard to develop more innovative statistical approaches to disentangling the complex web of interactions that are driving the birth outcomes. These innovations have been motivated by specific questions across all three projects.

Future Activities

In the upcoming year, we will continue to enroll study participants with our new target sample size of 1800 pregnant women. We will continue analyses on approximately 1250 participants with complete pregnancy data, genetic results, and environmental results already in hand. Analyses will look at the joint impact of environmental, social, and host factors on birth outcomes, especially as they differ by and within race. Identification of such co-exposures could lead to development and implementation of strategies to prevent adverse birth outcomes, ultimately decreasing or eliminating the racial disparity.

Statistical Methods Development. In the upcoming year, we plan to refine the Bayesian quantile regression with latent factors model, and extend it to include more data on host factors, in particular genetics data. We also will develop other flexible models for predicting birth outcomes besides quantile regression, including Bayesian density regressions. Finally, we will apply techniques that we have already developed for handling missing data and performing exploratory quantile regression to the augmented dataset (i.e., the additional births who enter the study), and develop new techniques as necessitated by future data collection.

Psychosocial Indicators. In year 4, we plan to incorporate the cluster analyses created from the psychosocial health variables into genetic and environmental analyses. In addition, we plan on examining the relationship between psychosocial health and the built environment.

Community Assessment Project/Built Environment. Imminent analyses will consider the broader suite of maternal psychosocial indicators, including stress, depression and anxiety. These analyses will be extended to include the psychosocial clusters previously developed and also how the intersection of built environment features and psychosocial status appears associated with maternal health behaviors.

*Environmental Sampling***.** In Year 4, we plan to pursue work similar to the lead analysis characterizing exposures to mercury and cotinine, including how maternal education and diet affects mercury levels as well as how cotinine levels are related to self-reported tobacco use and exposure to environmental tobacco smoke.

Roads . As indicated above, we are planning to run analysis that extends the road proximity work in Project A by incorporating the rich set of variables available in Project B, including analysis looking at how psychosocial health influences and gene-by-environment interactions may influence the impact of traffic-related air pollution on birth outcomes.

Publications – Accepted

Burgette, L. and Reiter, JP. Multiple Imputation via Sequential Regression Trees. Forthcoming, *American Journal of Epidemiology*.

Miranda, ML., Edwards, S., Paul, CJ., Swamy, G., Neelon, B. Blood Lead Levels among Pregnant Women: Historical Versus Contemporaneous Exposures, *International Journal of Environmental Research on Public Health, 7(4),* 1508-1519.

Swamy, GK, Garrett, ME, Miranda, ML, Ashley-Koch, AE. Maternal Vitamin D Receptor Genetic Variation Contributes to Infant Birthweight among Black Mothers. Forthcoming, *American Journal of Medical Genetics*.

Zhou, X. and Reiter, JP, (2010). A Note on Bayesian Inference after Multiple Imputation, *The American Statistician*, *64*, 159 - 163.

Publications – In Preparation/Submission

Ashley-Koch, AE, Garrett, ME, Swamy, GK, Miranda, ML. Genetic Variation in NAT1 Interacts with Cadmium Exposure to Influence Pregnancy Outcomes in Non-Hispanic Black (NHB) Women. In preparation.

Burgette, L. and Reiter, J. P. Exploratory Data Analysis for Quantile Regression: An Application to Adverse Birth Outcomes. In preparation.

Burgette, L. and Reiter, J. P. Quantile Regression with Latent Factors. In preparation.

Ingram, A, Maxson, P, Miranda, ML. Psychosocial Differences between Smokers and Non-smokers during Pregnancy. In preparation.

Maxson, P, Miranda, ML. Characterizing Pregnancy Intention. In submission.

Schwartz, S., Li, F., and Reiter, JP. Sensitivity Analysis for Unmeasured Confounding in Principal Stratification. In submission.

Swamy, GK, Garrett, ME, Miranda, ML, Ashley-Koch, AE. Genetic Variation in G-Protein Coupled Kinase Receptor 5 and Preeclampsia. In preparation.

Presentations

Ingram, A., Maxson, P., Miranda, ML. Psychosocial Differences between Smokers and Non-smokers during Pregnancy. American Public Health Association, Philadelphia, November, 2009.

Maxson, P., Miranda, ML. Pregnancy Intention, Risky Behavior and Birth Outcomes. Society for Maternal-Fetal Medicine, Chicago, February 2010.

Maxson, P., Miranda, ML. A Multidimensional Approach to Pregnancy Intention. American Public Health Association, Philadelphia, November, 2009.

Maxson, P., Miranda, ML. Pregnancy Intention, Maternal Psychosocial Health, Risky Behaviors, and Pregnancy Outcomes. Society for Epidemiologic Research, Anaheim, June, 2009.

Swamy, GK, Garrett, ME, Miranda, ML, Ashley-Koch, AE. Genetic Variation in G-Protein Coupled Kinase Receptor 5 and Preeclampsia. Society for Maternal-Fetal Medicine, Chicago, February 2010.

Supplemental Keywords
Pregnancy, preterm birth, low birth weight, racial disparity, African American, environmental stressors, gene-environment interactions, psychosocial stressors, genes, single nucleotide polymorphisms, genetic admixture

Research Project C: Perinatal Environmental Exposure Disparity and Neonatal Respiratory Health

Period covered by the report: 5/1/2009 – 4/30/2010
EPA Agreement Number: RD83329301-0
Investigators: P.I.: Richard L. Auten, Co-Inv: W. Michael Foster
Project Period: Year 3

Objectives of Research: Specific Aims

1. To determine whether maternal exposure to airborne particulates (PM) and/or ozone (1st hit) restricts fetal growth and/or postnatal growth, and impairs lung development/function in newborn mice;
2. To determine whether PM and/or ozone exposure 're-programs' maternal inflammatory responses;
3. To determine whether postnatal (2nd hit) ozone exposure further impairs postnatal somatic and lung development/function following maternal PM and/or ozone exposures;
4. To determine whether genetic or developmental susceptibility to airway hyperreactivity exacerbates maternal and/or postnatal exposure effects on postnatal somatic and lung development/function.

Progress Report/Summary of Accomplishments

1. Repeated exposures using spontaneously inhaled diesel particles generated from an internal combusion engine at US EPA have demonstrated dose-dependent augmentation on ozone-induced airway hyperresponsiveness.
2. This effect is sustained even after ceasing ozone exposure, since mice born to diesel exposed dams recovered for 4 weeks after neonatal ozone continue to demonstrate augmentation of airway hyperresponsiveness. This shows that prenatal diesel exposure has durable effects that persist to adulthood.
3. The diesel exposure appears to mediating these effects in utero, since pro-inflammatory cytokines are elevated in fetal lung, brain, and placenta harvested from fetuses exposed in utero to maternal diesel inhalation. The precise pathway is not yet known, but we are

currently conducting immunohistochemistry studies to identify the cellular compartments in the fetus that are affected first. This will allow us to design better studies to determine the path by which the pollutant affects fetal and neonatal development.

4. We have repeated the studies described above using diesel particles collected in collaboration with US EPA, and then instilled by tracheal insufflation during pregnancy, and found identical effects on fetal inflammatory cytokines in lung, placenta, and brain, as well as juvenile lung inflammatory cytokines. Most important, we found the same augmentation of ozone-induced airway hyperreactivity. This allows us to quickly move to more detailed analysis of the mechanism for pollutant effects without having to rely on ambient inhalation exposures, which cannot be accomplished at the desired rate because so many other investigators use the facilities.
5. Psychological stressors can contribute to the humoral and neural programming events in early life that would potentially affect a variety of the health outcomes we are studying. We have accordingly begun studies designed to mimic resource deprivation of nesting material during pregnancy and early postnatal rearing, as an analog to the stressors identified in Project A and B. Our preliminary studies in collaboration with Staci Bilbo, Dept. of Psychology & Neuroscience at Duke, demonstrate significant effects on postnatal weight gain in mice, and the addition of postnatal ozone increased mortality of pups to nearly 45%. We are presently conducting additional exposures at lower "doses" to determine if combined exposures to stresses below the typical effect threshold combine to yield an effect not seen with individual stressors. This new effort is funded in part by a new pilot grant through P30 ES-011961-01A1. An additional application through the Duke Integrative Brain Sciences program is pending, and a letter of intent has been submitted to the Department of Defense.
6. In order to determine whether the effects of combined pollutant exposure on airway hyperresponsiveness is mediated by changes in neural or airway smooth muscle programming, we evaluated the effects of immediate postnatal ozone exposure on airway mechanics in anesthetized mice, as well as in tracheal explants. We found that the airway hyperresponsiveness was not attributable to large effects on either airway smooth muscle bulk or on intrinsic airway smooth muscle responsiveness to neurotransmitter or electrical stimulation. There were some trends towards delayed relaxation in the ozone-exposed group. We next repeated the studies in animals that underwent cervical vagotomy at 6 weeks (2 weeks recovery after the 4 weeks of intermittent ozone exposure) just before measurement of airway mechanics. *We found that vagotomy eliminated the ozone-induced airway hyperresponsiveness*. This represents a paradigm shift of our understanding of the mechanisms by which ozone might affect asthma in children.

Collaborations with other SCEDDBO Components

1. Modification of study design: As noted above, the effects of resource deprivation suggested by findings in Projects A and B prompted us to add the resource deprivation (nesting restriction) component to Project C in order to test the proof-of-principle that the combination of multiple stressors/environmental contaminants may affect health even when the individual exposures do not.
2. Because the main findings in Project B pertain to fetal growth restriction and low birthweight, we are now designing studies in the animal model to mimic impaired uteroplacental insufficiency.

Future Activities

1. Determine whether the combination of ozone/diesel exposure with resource restriction impairs postnatal airway hyperresponse and postnatal cognition. Because the fetal brain

cytokine elevations following environmentally relevant diesel exposures were significant, we think it will be important to determine if there are neurobehavioral effects from the combined early-life contaminant exposures.

2. We will begin to develop a refinement of our multi-agent rodent models by adding uterine artery flow restriction in a rat model, or thromboxane infusion to the mouse model. Although all of our previous work has been done with the mouse models, the addition of fetal growth restriction is a critical component to achieving synergy across the projects. Fetal growth restriction and low birthweight are major outcome variables for Projects A and B. The mechanisms for these effects in humans more likely involve uteroplacental blood flow rather than caloric restriction.
3. Inflammation induced via the innate immune response has been previously linked to the development of ozone-induced AHR in adult mice. Inflammation is certainly present early in the ozone exposures in our juvenile exposure model as well, but we do not know if the innate immune system is important to the initial maternal inflammatory responses or the fetal inflammatory responses that may trigger the events leading to AHR in offspring. Accordingly we have begun a collaboration with John Hollingsworth, Dept. of Pulmonary and Critical Care Medicine at Duke, to conduct studies using Toll-like receptor 4 knockout (*Tlr4*$^{-/-}$) mice to delineate this pathway. Our first studies which have just begun, involve breeding null dams with wild-type sires in order to isolate the effects on *Tlr*4. We will determine whether maternal *Tlr*4 activation is required for the fetal inflammatory response independent of manipulation of *Tlr*4 in the fetuses, since all embryos will be phenotypically wild-type (*Tlr4*$^{+/-}$heterozygote).
4. Since epigenetic pathways are particularly likely biochemical transducers of environmental exposures on human disease, we have also begun a collaboration with Robert H. Lane, Professor of Pediatrics, University of Utah, who is a leader in this field. Our future studies will evaluate specific methylation targets relevant to air pollutant exposure using our mouse models. Since these pathways are also being explored in new collaborations begun in Project B, we expect these investigations to be mutually informative. In particular, low birth weight and fetal growth restriction appear to have epigenetic effects on brain glucocorticoid receptor gene which may link growth restriction (a focus of Project B) with some of the exaggerated stress responses in the pilot studies of the mouse models (Project C).

Publications – Accepted

Auten RL, Mason SN, Potts EN, Fischer BM, Huang Y, Foster WM. Maternal exposure to particulate matter increases postnatal ozone-induced airway hyperreactivity in juvenile mice. *Am J Resp Crit Care Med*. 2009. 180(12):1218-26. PMID 19762564

Auten RL and Foster WM. Biochemical Effects of Ozone on Asthma Development. Forthcoming, *Biochimica et Biophysica Acta*.

Publications – In Preparation/Submission

Auten RL, Mason SN, Potts EN, Gilmour MI, Foster WM. "Maternal Diesel Exhaust Particle Inhalation Durably Worsens Postnatal Ozone induced Airway Hyperreactivity in Mice. *In preparation*.

Presentations

Auten RL, Mason SN, Potts EN, Gilmour MI, Foster WM. “Maternal Diesel Exhaust Particle (DEP) Inhalation Worsens Postnatal Ozone induced Airway Hyperreactivity (AHR) in Mice” Pediatric Academic Societies, Baltimore MD, 2009.

Potts EN, Auten RL, Mason SN, Foster WM. Pulmonary Susceptibility of Neonatal Mice to Ozone Modulated by NQ01. American Thoracic Society International Conference, San Diego CA, 2009.

Supplemental Keywords
Airway hyperreactivity, diesel exhaust particles, air pollution, lung function

Annual Reporting Form for SCEDDBO Projects and Cores

Title of Project/Core: Community Outreach and Translation Core

Period covered by the report: 5/1/2009 – 4/30/2010
EPA Agreement Number: RD83329301-0
Investigators: Martha H. Keating
Project Period: Year 3

Objectives of Research

The central objective of the Community Outreach and Translation Core (COTC) is to create, implement, and assess strategies to translate and apply the findings of the Southern Center on Environmentally-Driven Disparities in Birth Outcomes (SCEDDBO) into relevant information for women of childbearing age, families, community groups, policy makers, and health care professionals. The COTC conducts environmental health outreach and education directed at low income and minority women and their children; enhances the capacity of disadvantaged communities to understand threats posed by environmental contaminants; and provides a bridge between campus research, communities and policy makers. The specific aims of the COTC are:

1. Support the community-based neighborhood assessment being undertaken as part of Research Projects A and B;
2. Partner with nursing programs at Duke-affiliated hospitals to develop and present curricula to nursing students on environmental exposures and maternal and child health outcomes;
3. Develop culturally-appropriate advisory materials on environmental contaminants for low-income expectant or nursing mothers with low English proficiency;
4. Deliver training to local health department personnel focused on environmental factors related to maternal health and pregnancy outcomes;
5. Participate in regional, state and federal policy dialogues to provide decision makers with policy-relevant science-based information concerning environmental exposures and health disparities related to maternal and child health and well-being; and

6. Increase awareness of maternal health and health disparities by facilitating bi-directional exchanges between Center investigators, community members, public health advocacy groups, and policy makers.

Progress Report/Summary of Accomplishments

The goals for COTC in Year 3 were to continue to expand communication and translation efforts to specific audiences. With a communication strategy in place, the COTC utilized various communication tools appropriate to a variety of audiences. Collaboration with researchers and groups external to SCEDDBO continued to evolve and the COTC welcomed and responded to requests for environmental health information from community groups and the general public.

In Year 3, the COTC continued to disseminate the findings of the Community Assessment Project (CAP) which assesses built environment variables for over 17,000 tax parcels, including the home addresses of over 40% of the participants in the Healthy Pregnancy, Healthy Baby Study (SCEDDBO Project B). During Year 3, the CAP report was distributed to nearly 250 community groups, Durham County and city officials, and community leaders (see (http://cehi.env.duke.edu/cap/). This distribution in turn led to numerous requests for COTC staff to present the findings of the study (see below under External Collaborations). In addition, the CAP methodology and findings were presented at the annual American Public Health Association meeting, EPA's environmental justice meeting, Strengthening Environmental Justice Research and Decision Making: A Symposium on the Science of Disproportionate Environmental Health Impacts, the Region 4 PEHSU Break the Cycle conference, and the 2010 Community Health Assessment Institute (Office of Healthy Carolinians).

Although data collection for CAP has concluded, the project is not static. CAP data are being summarized through the development of Neighborhood Health Indices which describe seven major characteristics of neighborhoods that potentially affect health (e.g., tenure, safety, housing and property damage). Development of the indices will facilitate linking the CAP findings to Projects A and B pregnancy outcomes.

Specific Aim 2 of the COTC is to partner with nursing programs to develop and present curricula to nursing students on environmental exposures and maternal and child health outcomes. Implementing activities to address this Specific Aim was a focus of COTC efforts in Year 3, and these efforts will continue in Year 4. A comprehensive project was designed to develop environmental health curricula for nursing students, nursing faculty, and practicing nurses. Supplemental funding was sought with a grant submittal to EPA's Environmental Education Grant Program. Funding determinations have not been announced at this time. The COTC also partnered with the UNC School of Nursing and Healthcare Without Harm to co-sponsor an environmental health symposium for practicing nurses. The symposium, Environmental Considerations in Nursing Practice attracted nationally-recognized speaker and an audience of 60 practicing nurses. The event was also accredited for Continuing Nursing Education credits. COTC staff participated in all aspects of the planning and execution of this conference. SCEDDBO Director Marie Lynn Miranda presented the keynote address.

Specific Aim 3 of the COTC is to develop culturally-appropriate advisory materials on environmental contaminants for low-income expectant or nursing mothers with low English proficiency. During Year 3 the COTC, guided by the communication strategy, established a number of dissemination efforts to distribute the mercury fish consumption fish advisory materials that were developed in Year 2 for Latino families. Because the materials will be

distributed to families primarily by nutritionists in the North Carolina Supplemental Nutrition Program for Women, Infants, and Children (WIC), considerable effort was expended to reach this audience. A series of webinars, accredited for continuing education credits for Registered Dieticians, were held for all WIC staff in North Carolina. The webinars were attended by 109 participants representing 66 out of 88 (80%) of the WIC clinics in North Carolina. A project description and all materials are also available on a newly-developed website (see http://cehi.env.duke.edu/fishadvisory/). In addition, the project was presented at two national conferences (American Public Health Association and the National Environmental Public Health Conference) and two program conferences sponsored by the National Institute of Environmental Health Sciences.

Specific Aim 4 of the COTC is to deliver training to state and local health departments focused on environmental factors related to maternal health and pregnancy outcomes. During Year 3, the COTC partnered with SCEDDBO's Geographic Information Systems and Statistical Analysis Core to offer no-cost training to public health professionals throughout North Carolina. Four all-day sessions of "An Introduction to GIS in Public Health: Tools for Mapping Social Determinants of Health" were held at the Nicholas School of the Environment. This course has broad ranging public health applications including policy guidance, community outreach and education, and program planning. The training was accredited for continuing education credits for Registered Sanitarians (the professional certification common to county health department personnel). The training courses were attended by 65 participants representing 18 NC counties, 18 different program areas of state government, 7 non-profit organizations, and Durham city personnel. The training courses not only build capacity within these organizations, but encourage future collaborations and networking between the COTC and stakeholder audiences.

COTC staff continues to collaborate with a variety of regional, state, and federal advisory groups including the American Lung Association Advisory Group, the Durham County Health Department Community Health Assessment Working Group, and the Obesity and Chronic Disease Committee of the Partnership for a Healthy Durham. In addition, SCEDDBO Director Marie Lynn Miranda was appointed to serve on the EPA's Children's Health Protections Advisory Committee (CHPAC). The CHPAC is a federal advisory committee established in 1998 to provide independent advice to the EPA Administrator on regulations, research, and communications issues relevant to children's environmental health.

Collaborations with other SCEDDBO Components

COTC staff continues to meet monthly with the SCEDDBO investigators to keep apprised of research developments and findings, translation opportunities, and scientific outreach activities (e.g., meetings, presentations and manuscripts) of the SCEDDBO investigators. The COTC staff also provides the investigators with updates on COTC activities and opportunities to participate in outreach activities. During Year 3, as part of the communication strategy, COTC staff received a periodic update from each SCEDDBO investigator detailing any presentations, conferences, or other issues or occasions that might constitute a research translation opportunity. These regular and frequent communications enable COTC staff to keep abreast of research progress, update the website, and plan for translation efforts.

External Collaborations

The COTC has developed a wide and diverse network of collaborators among federal, state and local agencies, universities and community groups. Activities with these diverse partners cover

a broad spectrum of children's environmental health issues, ranging from birth outcomes to lead poisoning prevention, environmental exposures, and obesity.

COTC staff has developed working relationships with scientists at the U.S. EPA representing a wide variety of disciplines. These relationships have allowed for exchange of research findings and data in a number of areas including distance-to-roadway analyses, air pollution impacts on birth outcomes, community engagement, and using GIS for environmental justice analysis. In terms of formal meetings, Dr. Marie Lynn Miranda was invited to present the keynote address at the joint NIEHS EPA meeting of the Gene and Environment Initiative's Exposure Biology Program. The meeting was held in August 2009 at the U.S. Environmental Protection Agency's campus in Research Triangle Park, North Carolina. Her talk entitled "Combining Population, Clinical, and Animal Models to Assess Exposure and Effects" described the research efforts currently underway at the Southern Center on Environmentally Driven Disparities in Birth Outcomes (SCEDDBO).

Activities with multiple state and local agencies continue to cover a wide variety of topics including the impact of the built environment on obesity and pregnancy outcomes, mapping environmental exposures and built environment variables, as well as other topics related to school-aged children. The COTC is actively working with staff at numerous state and local offices. At the state government level these offices include the Senior Advisor for Healthy Schools, the Women's Health Branch, the Nutrition Services Branch, and the Office of Healthy Carolinians. Activities with county health departments and non-profit organizations ranged from GIS training and fulfilling mapping requests to serving on advisory groups (for example Durham County's Community Health Assessment Working Group).

For the 2nd consecutive year COTC investigators mentored a student in the "Break the Cycle" project sponsored by the Region 4 of the U.S. EPA, Emory University and the Southeast Pediatric Environmental Health Specialty Unit. The selected student used data from SCEDDBO's Healthy Pregnancy Healthy Baby research project to describe the effects of maternal depression on pregnancy outcomes. These findings were presented at the 4th Break the Cycle in September 2009. Also in year 3, the next round of "Break the Cycle" was underway. The selected student for this round explored the relationship between the built environment and low birthweight. These findings will be presented May 6, 2010 (year 4) at Emory University in Atlanta.

A major focus of the COTC continues to be dissemination of the findings of the Community Assessment Project. Outreach meetings were held with various and diverse community and neighborhood groups and other interested parties, ranging from the Southwest Central Durham Quality of Life Project in southwest Durham to singer Jackson Browne. In addition, COTC staff have participated in and provided GIS and other support to a range of other community stakeholders including the Durham Police Department, NC Legal Aid, Clean Energy Durham and Durham Congregations, Associations and Neighborhoods, among others.

Finally, the COTC continues to respond with detailed information to numerous requests from private citizens about a variety of environmental health concerns. These requests were received through both the CEHI toll-free number and via the CEHI website.

Future Activities

During year 4, the COTC will continue to expand communication and translation efforts to specific audiences. By participating in the design, planning, and execution of the Durham County Community Health Assessment, we hope to gain additional insight into community health and information needs. We will also continue our efforts to incorporate environmental health topics into continuing nursing education and sustain established collaborations with researchers within and external to SCEDDBO.

Publications

Presentations

Keating, MH, L Richardson,T Connaughton-Espino. Hook, Line, and Sinker: Developing, Delivering, and Testing Fish Advisory Messages for Latinas. 2009 National Environmental Public Health Conference, Atlanta, GA, October 28, 2009.

Keating, MH, L Richardson, T Connaughton-Espino, ML Miranda. Delivering Complex Environmental Messages in Cultural Context. 137th Annual APHA Meeting, Philadelphia, PA. November 7-11, 2009. (poster).

Kroeger, GL, ML Miranda, J Davis. Community Assessment: Understanding the Built Environment with a Neighborhood Health Context. 137th Annual APHA Meeting, Philadelphia, PA. November 7-11. 2009.

Kroeger, GL, The CEHI Community Assessment Project: A Tool for Linking the Built Environment with Key Health Outcomes. Strengthening Environmental Justice Research and Decision Making: A Symposium on the Science of Disproportionate Environmental Health Impacts, Washington, DC. March 17, 2010. (Poster)

Modlin, E., Maxson, P. Breaking the Cycle of Maternal Depression: An Initiative to Improve Children's Environmental Health. Break The Cycle, Atlanta, September, 2009.

Supplemental Keywords

Risk communication, outreach, translation, participatory research, built environment

Geographic Information System and Statistical Analysis Core

Period covered by the report: 5/1/2009 – 4/30/2010
EPA Agreement Number: RD83329301-0
Investigators: Alan Gelfand (PI), Allison Ashley-Koch, Marie Lynn Miranda, Jerome Reiter
Project Period: Year 3

Objectives of Research

The overall objective of the GIS and Statistical Analysis Core is to **support spatial and quantitative analysis needs of the Center research projects, as well as the Community Outreach and Translation Core.** Our specific aims include:

1. Providing support for the development of environmental and social data layers needed to implement data analyses required for the research projects and the Community Outreach and Translation Core;

2. Providing statistical analysis, advice, and consulting on the broad range of statistical issues that arise in conjunction with the research projects, with a particular emphasis on data reduction methods and modeling spatial and spatio-temporal data within a Bayesian framework; and,

3. Providing analysis for the unique needs of genetic data arising from the clinical and animal studies of the center.

This support core facilitates the development of innovative quantitative methodology for children's environmental health research associated with the projects and cores. Equally important, it will enhance substantive collaboration between statisticians and scientists involved in the research projects yielding improved analyses of research core data, as well as novel statistical modeling.

Progress Report/Summary of Accomplishments

In the third year of the project, the GISSA Core has continued to focus on developing the data warehouse providing underlying support for all other Center components. We have acquired and georeferenced additional detailed birth record data, continued genotyping blood samples from the participants in Project B, and continued providing data management support as Project B continues to enroll additional participants.

We now have in hand identified North Carolina Detailed Birth Records (DBR) at the individual subject level, giving us access to 18 years of birth data covering 1990-2008. The DBR is compiled from questionnaires obtained at the time of birth certificate filing and includes elements essential to our proposed analyses. Available variables include, *inter alia*: maternal residence and state and country of birth; marital status; maternal and paternal race, Hispanic ethnicity, and education; alcohol and tobacco use; plurality; parity; maternal complications; congenital anomalies; whether an infant death certificate was filed; and infant birth weight and gestational age. All 18 years of data have been integrated and standardized to facilitate data linkages and statistical analysis.

In addition to incorporating the most recently available North Carolina DBR data into the GISSA Core data warehouse, we have also worked to acquire additional birth data that will enhance

various research projects across SCEDDBO. We have received historical NC DBR data for 1978-1989. Although this data does not contain all the detail available in more recent years, such historical data will enable us to examine trends in birth outcomes across the state. Additionally, we have initiated communication with the vital records offices of the other states in Region 4 in order to explore the acquisition of birth data in these states.

We have expanded the environmental data layers available for use through the SCEDDBO data warehouse. These include spatial data on road intensity, criteria air pollutants from the USEPA's AQS system, water quality, environmental releases documented in the Toxics Release Inventory, and housing quality.

We have developed methods for linking the North Carolina DBR data with participant data from Project B. All participants who delivered between 2005 and 2008 have been successfully matched to their corresponding record in the DBR. This linkage will allow us to examine how accurately the administrative dataset (DBR) captures key information, as well as undertake analysis of residential mobility during pregnancy. In addition, as more years of DBR data become available, we will be able to find future births to Project B participants and examine internatal spacing and subsequent pregnancy outcomes.

To date, we have genotyped 1243 blood samples from pregnant women for 405 Single Nucleotide Polymorphisms (SNPs) in fifty-one genes, primarily involved in either metabolism of heavy metals or immune response. In addition, we have generated the Illumina African American Admixture Chip on 824 NHB women. With these data now available, we have begun statistical analysis looking at environmental and genetic contributions and interactions to pregnancy outcomes. These results are discussed in the Project B report. We anticipate further genotyping and statistical analysis in the coming year.

Collaborations with other SCEDDBO Components

By its nature, the GISSA Core is highly involved in collaborations across all Center components. We are working with the investigators of Project A to determine what spatial data layers need to be developed and at what spatial scales. We are also expanding and supporting the data architecture to facilitate linkages of the data compiled by Projects B and C in order to create opportunities for synergies across projects.

Future Activities

We will continue developing and expanding the geospatial data warehouse that supports analysis among various projects. The GIS team will continue working with investigators in Projects A and B to develop a comprehensive list of environmental spatial data layers of interest, as well as a plan for prioritizing the development of this crucial dataset.

We will continue analyses on approximately 1,200 Project B participants with complete pregnancy data, genetic results, and environmental results. Analyses will look at the joint impact of environmental, social, and host factors on birth outcomes, especially as they differ by and within race. Identification of such co-exposures could lead to development and implementation of strategies to prevent adverse birth outcomes, ultimately decreasing or eliminating the racial disparity. We will also continue to generate imputed datasets based on the methodology developed by the GISSA Core, in order to handle missing data.

As Project B continues to enroll participants, maternal blood samples will be analyzed for genetic and gene x environment associations with adverse birth outcomes. Additional genotyping will involve genes in the maternal stress response and vascular/endothelial cell

dysfunction pathways. Statistical analysis regarding candidate gene polymorphisms has already begun and will continue in Year 4.

Publications
All manuscripts supported by the GISSA Core are listed under the individual research projects.

Supplemental Keywords
Data fusion, meta analysis, disparities, spatial disaggregation, spatial interpolation, spatial modeling